


## PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT  
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P045108PCT DBO/do		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/NL 03/00420	International filing date (day/month/year) 11.06.2003	Priority date (day/month/year) 11.06.2002	
International Patent Classification (IPC) or both national classification and IPC A61K31/567			
Applicant PANTARHEI BIOSCIENCE B.V. et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand  12.01.2004		Date of completion of this report  06.09.2004	
Name and mailing address of the International preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer  Klaver, J  Telephone No. +49 89 2399-8601	



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/NL 03/00420**

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-17 as originally filed

**Claims, Numbers**

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY  
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**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes: Claims	1 - 16
	No: Claims	
Inventive step (IS)	Yes: Claims	1 - 16
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1 - 16
	No: Claims	

**2. Citations and explanations**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/NL 03/00420

1). The prior art does not disclose methods for treating skin or formulations for topical administration comprising an estrogenic compound of the formula as given in claim 1. Uses of such a compound in the manufacture of compositions as defined in claims 12 - 14 have not been disclosed either.

The subject-matter of claims 1 - 16 hence is novel (Art. 33 (2) PCT).

2). The advantageous effects of (topically administered) estrogens, in particular of estriol and estradiol, on skin aging, vaginal dryness and wound healing are well-known in the art as can be seen from the Y-documents cited in the International Search Report.

Estriol, the weaker estrogen as compared to estradiol, is considered the preferred estrogen for topical use in the treatment of skin aging (Schmidt et al., 1996 (= D3): Discussion, page 673, col. 1, last paragraph) and is used in D3 at a concentration of 0,3% in skin treatment creams.

Estretol, the preferred compound as used in the present application, also is a weaker estrogen as compared to estradiol (see, e.g., Table 2 of the application and the citations on pages 4 and 5 of the present description).

Mueck et al., 2001 (D5) disclose, that the effect of estretol on endothelial cell growth in umbilical veins is of the same order as that of estriol, but are silent on possible effects on skin aging.

The present application demonstrates, that estretol may be used at a concentration of 0,1% in topical creams, resulting in positive effects in patient's appearance, vaginal dryness and various quantitative parameters (examples 3 - 6).

The available prior art does not disclose or suggest, that such positive effects could be obtained with creams at a concentration level of estretol substantially lower than that of the closely related estriol compound as used in D3.

The subject-matter of present claims 1 - 16 hence is considered to be based on an inventive step (Art. 33 (3) PCT).

3). The industrial applicability is evident (Art. 33 (4) PCT).